

PTO 09-0354

CC=JP  
DATE=19880727  
KIND=A  
PN=63182304

MICROCRYSTALLINE CHITOSAN AND ITS MANUFACTURE  
[BIKESSHO KITOSAN OYABI SONO SEIZO HOHO]

HIROSHI YOKOTA

UNITED STATES PATENT AND TRADEMARK OFFICE  
WASHINGTON, D.C. OCTOBER 2008  
TRANSLATED BY: SCHREIBER TRANSLATION, INC.

PUBLICATION COUNTRY (10): JP  
DOCUMENT NUMBER (11): 63182304  
DOCUMENT KIND (12): A  
PUBLICATION DATE (43): 19880727  
APPLICATION NUMBER (21): 62-13834  
APPLICATION DATE (22): 19870123  
INTERNATIONAL CLASSIFICATION (51): C 08 B 37/08 ; //A 61  
K 35/56 ; C 09 K 3/00  
PRIORITY COUNTRY (33): NA  
PRIORITY NUMBER (31): NA  
PRIORITY DATE (32): NA  
INVENTOR(S) (72): YOKOTA, HIROSHI  
APPLICANT(S) (71): DAICEL CHEMICAL  
INDUSTRIES, LTD.  
DESIGNATED CONTRACTING STATES (81): NA  
TITLE (54): MICROCRYSTALLINE  
CHITOSAN AND ITS  
MANUFACTURE  
FOREIGN TITLE [54A]: BIKESSHO KITOSAN  
OYABI SONO SEIZO HOHO

Specification

1. Title of Invention

Microcrystalline Chitosan and its Manufacture

2. Claim

1. Microcrystalline chitosan having a limit viscosity number of 1.5 to 2.0 dl/g which measures a 1 % acetic acid aqueous solution as a solvent; the x-ray method degree of crystallinity is within the range of 80 to 90%;
2. A method for manufacturing crystalline chitosan characterized as partially hydrolyzing the chitosan by using a group made up of organic solvent-water-mineral acid;
3. A method for manufacturing crystalline chitosan as described in Claim 2 wherein the abovementioned organic solvent is a water-soluble solvent;
4. A method for manufacturing crystalline chitosan as described in Claim 3 wherein the abovementioned organic solvent is an alcohol;
5. A method for manufacturing crystalline chitosan as described in Claim 2 wherein the abovementioned mineral acid is hydrochloric acid, sulfuric acid or nitric acid;
6. A method for manufacturing crystalline chitosan as described in Claim 3, Claim 4 or Claim 5 which uses 300 to

1,000 wt parts of the abovementioned organic solvent, 300 to 1,000 wt parts of water and 100 to 200 wt parts of mineral acid relative to 100 wt parts of chitosan in manufacturing using the abovementioned partial hydrolysis.

### 3. Detailed Description of Invention

#### (Industrial Use)

The present invention relates to crystalline chitosan and a method for manufacturing it. It relates more particularly to a crystalline chitosan which is obtained by removing the amorphous part of the chitosan obtained by separation from a natural substance using acid hydrolysis and a method for manufacturing same.

#### (Prior Art)

O.A. Battista's "Microcrystal Polymer Science", McGraw Hill (1975) describes in detail the properties and the method of manufacturing a variety of crystalline polymers obtained by removing the crystalline parts by removing the amorphous parts using acid hydrolysis from substances such as polymer Cellulose, amylase, chitin, collagen and other

crystalline natural polymer substances as well as polyamide, polyester, polyolefin and other crystalline synthetic polymers having a crystalline part and an amorphous part.

Of these microcrystalline polymers, it is possible to pressurize and mold those having common characteristics of hydrophilic polymers and it is easy to make them gels when the water dispersed element of a microcrystal polymer is subjected to high-speed stirring under shearing.

Meanwhile, chitosan which is obtained from chitins which are distributed widely in nature as tissue supports for crustaceans and insects as well as deacetylation of these chitins has been garnering attention in recent years as a functional material in many fields, first and foremost in the medical field and research is being carried out proactively on these. Chitosan has a free amino group so that a variety of functional manifestations are expected as cationic polymers. However, since an acid and an acid salt which makes contact with this are formed and dissolved in water, the abovementioned microcrystalline polymer

manufacturing method cannot be applied and there is no prior art which has obtained the chitosan as microcrystals.

(Problems Which the Present Invention is Intended to Solve)

Even when attempts are made to carry out acid hydrolysis on chitosan based on the prior art using a nonuniform group, the chitosan dissolves and becomes a uniform group. The decomposition proceeds and decomposition is carried out as far as 2-amino-2-deoxy-D-glucose whether these are crystalline parts or amorphous parts and microcrystalline chitosan cannot be obtained.

The present invention has solved the prior-art problems indicated above and provides microcrystalline chitosan with outstanding uses and a method for manufacturing same.

(Means Used to Solve the Problems)

The inventors found that when chitosan was processed in a suitable organic solvent-water-mineral acid group, acid hydrolysis could be carried out in a non-uniform chitosan group and that the crystal part could be recovered as a microcrystalline chitosan using this and they achieved the present invention.

It is well known that microcrystalline chitosan which is obtained by processing the chitosan in an organic solvent-water-mineral acid group and removing the amorphous part is a fine powder. When its physical properties are compared with those of raw material chitosan, the degree of polymerization is low, it is made uniform and the degree of crystallinity increases.

(Constitution of Invention)

The present invention relates to a microcrystalline chitosan whose limiting viscosity number is in the range of 1.5 to 2.0 dl/g which measures a 1 % acetic acid aqueous solution as a solvent and the x-ray method degree of crystallinity is in the range of 80 to 90 %.

The present invention relates as well to a method of manufacturing microcrystalline chitosan wherein the chitosan is partially hydrolyzed using an organic solvent-water-mineral acid group.

Chitosan which is the raw material for the microcrystalline chitosan in the present invention can be obtained by refining the shells of crustaceans such as

shrimp and crab and flaky chitosan which has been refined using this method is commercially available.

In the method of manufacturing in the present invention, the organic solvent used for acid hydrolysis of the raw material chitosan should be compatible in water and alcohols, ketones and the like are suitable. n-propanol, iso-propanol, n-butanol, sec-butanol, iso-butanol, tert-butanol and the like are especially suitable. These solvent have good compatibility in water and the relative boiling point is high so that the reaction temperature can be set high and the reaction can be carried out in a short period of time.

The mineral acid used in the manufacturing method in the present invention may be hydrochloric acid, nitric acid, phosphoric acid and the like.

The method of manufacturing in the present invention may be carried out as follows using a suitable mode.

We mixed the chitosan and the following substances in the amount indicated (in all cases, amounts are relative to 100 wt parts of chitosan):

Organic solvent	300 to 1,000 wt parts
Water	300 to 1,000 wt parts
Mineral acid	100 to 200 wt parts

and placed them all in a hydrolysis container and stirred them for 0.5 to 2 hours at a reflux temperature (85 to 90°C). The acid hydrolysis of the chitosan was completed using the abovementioned processing. Next, we cooled this group to room temperature and filtered it. We placed the coarse microcrystalline chitosan obtained in 1,000 wt parts of the same type of organic solvent as was used for the hydrolysis. When we stirred it at room temperature for 15 to 30 minutes and filtered it, we obtained a fine powder product which was wet. This was microcrystalline chitosan

/3

from which most of the mineral acid which had adhered was removed. We placed this in a solution made up of 30 wt parts of caustic soda, 1,500 wt parts of water and 1,500 wt parts of organic solvent (this should be the same type of solvent as was used for the hydrolysis) and stirred it for 15 to 30 minutes at room temperature and neutralized the acid which had been added to the acid which had adhered and the amino group. After this, we washed the microcrystalline chitosan until the washing solution was neutral. After we

washed it, we dried the microcrystalline chitosan. The function manifestation of the microcrystalline chitosan is influenced by this drying method.

Suitable modes of drying are: (1) freeze-drying; (2) drying at 50 to 60°C after water has been substituted using an organic solvent; and (3) spray-drying. When drying is carried out using the method in (1) or (2), secondary aggregation takes place and the fine powder becomes a lump. The desired microcrystalline chitosan is obtained by pulverizing the lumpy dried product. Usually at least 90 % of fine powder can be obtained having a grain size of not more than 60  $\mu$  m.

#### [Effect of Invention]

The microcrystalline chitosan which can be obtained by using the method in the present invention can be compression-molded and tablets consisting of this can be molded. As a result, it can be used as a tablet-form combined excipient and disintegrator. Its disintegrating characteristics when used for tablets for medicine are superior to those of microcrystalline cellulose. In addition, when the microcrystalline chitosan is suspended in water and stirred at a high shear force, the suspension

group has the form of a sticky gel so that it can be added to food and used as an excipient. In addition, the abovementioned gel substance is spread using an applicator on a glass plate. When it dries, it can be used as a thin layer chromatography support.

(Practical Examples)

Next, we shall describe the present invention in greater detail by using practical examples of it.

Practical Example 1

We placed 100 g of commercially available chitosan flakes (manufactured by Kyowa Yushi (Ltd.),  $[\eta]_1^1$  acetic acid = 141, degree of crystallinity 60 %) in a mixed solution of 524 g of isopropanol (IPA), 60 g of water and 478 g of 36 % hydrochloric acid. We heated this to a reflux temperature ( $87^\circ\text{C}$ ) and kept it for 30 minutes while stirring it. Then, we cooled it, filtered it and placed the coarse microcrystalline chitosan in 1,000 g of IPA and stirred it at room temperature for 30 minutes. Then, we filtered it and placed the solid part in a mixed solution of 30 g of caustic soda, 1,500 g of water and 1,500 g of IPA and processed for 30 minutes at room temperature. After we processed it, we washed it with water, carried out

acetone substitution, dried it and pulverized it and obtained 70 g of a microcrystalline chitosan powder ( $[\eta]_{\text{H}_2\text{O}} = 1.9$ , degree of crystallinity 85 %, more than 95 % having grain size of  $60 \mu\text{m}$  and under).

### Practical Example 2

We carried out the same processing on the same chitosan flakes used in Practical Example 1 using the same method as Practical Example 1 under the same conditions except that we changed only the hydrolysis time to 1 hour and 30 minutes. Then, we carried out exactly the same post-processing, drying and pulverizing as in Practical Example 1 and obtained 60 g of a microcrystalline chitosan powder ( $[\eta]_{\text{H}_2\text{O}} = 1.9$ , degree of crystallinity of 87 %, more than 95 % having a grain size of  $60 \mu\text{m}$  and under).

### Practical Example 3

We placed 100 g of the same chitosan flakes which we used in Practical Example 1 in a mixed solution of 524 g of isopropanol, 219 g of water and 319 g of 36 % hydrochloric acid. We heated this to a reflux temperature ( $88^\circ\text{C}$ ) and held it for one hour while stirring. The post-processing following this was carried out exactly as in Practical Example 1 and we obtained 73 g of a microcrystalline powder

( $[\eta]$  1% acetic acid = 2.0, degree of crystallinity 80 %, more than 90 % having grain size of 60  $\mu$  m and under).

#### Practical Examples 4 and 5

We made an aqueous suspension using the microcrystalline chitosan obtained in Practical Example 1 and stirred it using a homomixer at 10,000 rpm and obtained a sticky gel. The viscosity of the gel obtained was measured using a model B viscometer (rotor No. 4, 60 rpm, 25°C). Results are indicated in the following table.

	Practical Example 4	Practical Example 5
Microcrystalline chitosan concentration (wt %)	12	15
Viscosity (cps)	1.990	4.220